

REMARKS

New claims 39-81 have been added. Support for the new claims can be found throughout the specification, including for example at pages 4-5, and in the previously presented claims. No new matter has been added by the amendments.

Claims 18-81 are pending in the application, with claims 18, 34, 39, 58 and 66 being the independent claims. Claims 34 and 38 have been withdrawn from consideration by the Examiner.

I. Statement of Substance of the Interview

Applicants thank Examiners Liu and Wyrozebski for the personal interview conducted on August 24, 2010, with Applicants' undersigned representatives. During the interview, the rejections of record were discussed, as well as whether or not Zimmerman and Huang are combinable. Potential amendments as well as declarations to overcome Huang were also discussed. No conclusive agreement was reached.

II. The Rejection of Claims 18-19 and 21-27 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 18-19 and 21-27 have been rejected at pages 3-4 of the Office Action as allegedly being unpatentable over Zimmermann, U.S. Patent No. 6,465,226 (hereinafter "Zimmermann") in view of Huang *et al.*, *Solid State Ionics* 120:205-210 (1999) (hereinafter "Huang"). Applicants respectfully traverse this rejection.

The Office Action suggests that Zimmermann discloses a process for preparing microspheres comprising an ionically crosslinked polymer, the process comprising producing liquid droplets from a solution comprising an ionically crosslinkable polymer into a gas stream using a nebulizing nozzle, and transferring the gas stream into a gelling solution.

The Office Action concedes that Zimmermann does not teach using an ultrasonic nebulizer to form the gas stream. The Office Action attempts to cure this deficiency with the disclosure of Huang, asserting that Huang discloses a process for preparation of a homogeneous,

ultrafine powder by generating an aerosol with an ultrasonic nebulizer. The Office Action indicates that it would have been obvious to employ the ultrasonic nebulization method of Huang in Zimmerman, as Huang discloses that atomizing a precursor solution by ultrasonic nebulizer produces homogenous, ultrafine powders having a particle size of about 100 nm. The Office Action also indicates that Zimmermann does not explicitly disclose separating the microspheres from the gelling solution. However, the Office Action suggests that it is inherent that the microspheres are separated from the gelling solution in Zimmermann. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

A) The Combination of Zimmermann and Huang Do Not Disclose the Present Claims

As an initial point, Applicants respectfully submit that Zimmermann as modified by Huang does not disclose “transferring the gas stream into a gelling solution comprising di-, multi- or polyvalent ions, whereby crosslinked polymer microspheres are formed,” of present claim 18. Rather, Zimmermann discloses that “the alginate solution [is] dropped into a Petri dish” (*see* Zimmermann at column 3, lines 15-16), which provides the precipitation bath. Applicants submit that a person of ordinary skill in the art would understand that “dropping” the droplets from the nozzle of Zimmerman into the gelling solution is not the same as “transferring the gas stream into” the gelling solution of present claim 18, which clearly requires that the gas stream *enter into* the gelling solution, rather than simply allow droplets in the gas stream to drop *onto the surface* of the gelling solution, as set forth in Zimmermann. Applicants submit that Huang provides no indication of how a nebulized solution should be transferred to another solution.

Applicants respectfully submit that a person of ordinary skill in the art would understand that simply dropping nebulized droplets onto the surface of a gelling solution, as suggested by Zimmermann, would most likely not actually allow the nebulized droplets to enter the gelling solution, as required by the presently claimed invention. Production of droplets via nebulization results in a “mist” of droplets that, if simply dropped onto the surface of a gelling solution would most likely simply float above the surface of the liquid (as in an air humidifier), or produce a film on top of the gelling solution, thus not allowing for the formation, and ultimate separation,

of polymer microspheres. Applicants submit that the combination of Zimmerman and Huang does not disclose all of the required elements of the presently claimed invention. Thus, Applicants submit that the Office Action as not set forth a *prima facie* case of obviousness. See M.P.E.P. § 2143.03.

B) There Is No Reasonable Expectation of Success in Combing Zimmermann and Huang

Applicants also respectfully submit that there is no reasonable expectation of success that the atomic nebulizer disclosed in Huang could be utilized in the methods of Zimmermann to produce droplets of islets of Langerhans having the size required in Zimmermann. Zimmermann requires that the formed droplets have a diameter that is 1.5 to 4 times the volume of biologically active substance (islets of Langerhans) that form the cores of the microcapsules. See Abstract. This requirement is met by providing the appropriate conditions of air flow and flow rate. *Id.* Applicants submit that there is no indication that the ultrasonic nebulizer disclosed in Huang could produce droplets having the required size characteristics, or even produce droplets of the islets of Langerhans at all.

The ultrasonic nebulizer disclosed in Huang is designed to generate an aerosol of an alcoholic precursor solution that is carried to an ignition nozzle of a flame spray pyrolysis setup, where the aerosol is ignited so as to form an ultrafine powder on the wall of the collector. See Huang at page 206, Experimental aspects. In Huang, a precursor solution comprising SnCl_4 or SnCl_2 dissolved in ethanol is aerosolized. Applicants submit that there is not a reasonable expectation of success that simply because the ultrasonic nebulizer in Huang is able to generate an aerosol of these particular materials that it in any way could generate droplets of islets of Langerhans having the requisite diameter of 1.5 to 4 times the volume of the core of biologically active material. As set forth in M.P.E.P. § 2143(D), a *prima facie* case of obviousness can only be shown where the cited combination of references would yield predictable results. See *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007). The Office Action has not provided a showing that modifying the disclosure of Zimmermann with that of Huang would have a reasonable expectation of success -- i.e., a reasonable expectation of producing the droplets required in the methods of Zimmerman. Absent such a showing, a *prima facie* case of obviousness cannot be established. See M.P.E.P. § 2143.02.

C) Huang Would Render Zimmermann Unsatisfactory for Its Intended Purpose

In addition, Applicants submit that Zimmermann cannot be modified with the disclosure of Huang, as required in Office Action, as such a modification would render Zimmermann unsatisfactory for its intended purpose. As set forth in M.P.E.P. § 2143.01, “[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants submit that Zimmermann is directed to the production of microcapsules containing the biologically active material, islets of Langerhans. As noted in Zimmermann, these cells produce insulin, and it is a goal of Zimmermann to “introduce living cells into the human body,” so as to treat diabetes mellitus. *See* Zimmermann at column 1. To encapsulate these cells, it is first necessary to generate droplets of the cells. While Zimmermann utilizes a spray nozzle which focuses airflow to generate the droplets (*see* Zimmermann at column 3, lines 1-5), the Office Action suggests that a person of ordinary skill in the art would have found it obvious to instead utilize the ultrasonic nebulizer of Huang to form the droplets.

Applicants respectfully disagree with this suggestion and note that a person of ordinary skill in the art would not have considered it obvious to utilize the ultrasonic methods of Huang to generate the droplets required in Zimmermann. At the time of filing the present application it was well known that, due to the fragility of islets of Langerhans, application of ultrasound actually *disrupts* the islets, and specifically, the β -cell structure. *See, e.g.,* Parry *et al.*, “Proinsulin Biosynthesis in Broken-Cell Preparations of Islets of Langerhans,” *Biochem J.* 170:523-527 (1978) (copy attached as Exhibit A). As discussed in Parry, subjecting islets of Langerhans to ultrasound of 1 MHz for 2 seconds (*see* Parry at page 524, first paragraph), destroys the islets and their enzymic machinery. “It may be concluded that when β -cells are disrupted by ultrasonic methods the enzymic machinery for converting proinsulin to insulin is disorganized . . . [m]icroscopic examination of the cells, moreover, did not suggest the presence of any intact cells in the preparation.” *Id.* at page 526, first column.

Thus, a person of ordinary skill in the art clearly would not have considered it obvious to utilize the ultrasonic nebulizer of Huang, which operates at a similar frequency of 1.63 MHz (*see* Huang at page 206, Experimental aspects) in the methods of Zimmermann, as ultrasound in this range, as demonstrated by Parry, destroys islets of Langerhans and their enzymic machinery. In fact, due to an increased dwell time in the ultrasonic nebulizer that would clearly be longer than the 2 seconds utilized in Parry, a person of ordinary skill in the art would clearly expect such a treatment to destroy, or at least inactivate, the islets. As Zimmermann is directed to methods of encapsulating active cells (i.e., intact, enzymically active), such a modification would clearly render Zimmermann unsatisfactory for its intended purpose. As set forth in M.P.E.P. § 2143.01, such a modification is not allowed, and thus, the Office Action has not set forth a proper *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

III. The Rejection of Claims 20 and 28 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 20 and 28 have been rejected at pages 4-6 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and further in view of Lim, U.S. Patent No. 4,352,883 (hereinafter “Lim”). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann and Huang disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the polyvalent cation of the gelling solution is selected from the compositions set forth in present claim 20, or that the metal cation is Ca²⁺, as set forth in present claim 28. The Office Action attempts to cure these deficiencies with the disclosure of Lim, suggesting that Lim discloses the polyvalent cation polyethyleneimine of a gelling solution and the use of Ca²⁺ as the metal cation of a gelling solution. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Lim fails to cure these deficiencies as it provides no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann. Thus, Zimmermann, Huang and Lim, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

IV. The Rejection of Claims 29-30, 32 and 35-37 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 29-30, 32 and 35-37 have been rejected at pages 6-7 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and further in view of Andersson *et al.*, Published International Patent Application No. WO 03/091315 (hereinafter “Andersson”). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann and Huang disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the gelling solution additionally comprises surfactant present in an amount of from 0.05% to .15% by weight; that the solution of the ionically crosslinkable polyionic polymer is kept within a temperature range of 25 to 35°C; or filtering the microspheres through a screen. The Office Action attempts to cure these deficiencies with the disclosure of Andersson, indicating that Andersson discloses the addition of surfactant to a gelling solution, and the use of a temperature of 40°C, and filtering beads through a sieve. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Andersson fails to cure these deficiencies as it provides no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of

Zimmermann. Thus, Zimmermann, Huang and Andersson, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

V. The Rejection of Claim 31 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 31 has been rejected at pages 7-8 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and Andersson and further in view of Lemoine *et al.*, *International Journal of Pharmaceutics* 176:9-19 (1998) (hereinafter “Lemoine”). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang and Andersson disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the surfactant is selected from those compositions set forth in present claim 31. The Office Action attempts to cure these deficiencies with the disclosure of Lemoine, indicating that Lemoine discloses the use of polyoxyethylene sorbitan trioleate as a surfactant in the production of alginate microspheres. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Andersson and Lemoine fail to cure these deficiencies as they provide no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann. Thus, Zimmermann, Huang, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

VI. The Rejection of Claim 33 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 33 has been rejected at pages 8-10 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and further in view of Vasington *et al.*, U.S.

Patent No. 5,387,522 (hereinafter “Vasington”), Anderson and Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Andersson and Lemoine disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the solution comprises 0.75% to 1.5% by weight of sodium alginate. The Office Action attempts to cure these deficiencies with the disclosure of Vasington, indicating that Vasington discloses the use of low viscosity sodium alginates at about 0.5% to about 1.4%. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Vasington, Andersson and Lemoine fail to cure these deficiencies as they provide no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann. Thus, Zimmermann, Huang, Vasington, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

VII. New Claims 39-81

Applicants respectfully submit that for at least the reasons set forth above, newly added claims 39-81 are not anticipated or rendered obvious by any of the references cited in the Office Action.

Applicants submit that none of the references cited in the Office Action disclose the claimed methods wherein the gas stream is submerged into a gelling solution comprising di-, multi- or polyvalent ions, whereby crosslinked polymer microspheres are formed. Specifically, with regard to Zimmermann, Applicants note that this reference discloses that the droplets of islets of Langerhans are “dropped into a Petri dish” which acts as the precipitation bath. *See* Zimmermann at column 3, lines 15-16. Thus, Zimmermann does not disclose submerging the

gas stream into the gelling solution, and thus, the presently claimed invention is not anticipated or rendered obvious by this or any of the references cited in the Office Action.

VIII. Conclusion

Applicants believe that the claims of the present application are in condition for allowance and respectfully request allowance thereof. The Examiner is invited to telephone the undersigned if that would be helpful in resolving any issues.

With the exception of extension of time fees, no fees are believed due for this submission. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application or credit any overpayment, to Deposit Account No. 50-5071. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-5071.

Respectfully submitted,

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By: 

FANELLI, STRAIN & HAAG PLLC
Customer No. 0091436
1455 Pennsylvania Avenue, N.W.
Suite 400
Washington, D.C. 20004
Telephone: 202.621.1840
Facsimile: 202.621.1844

Paul D. Strain
Registration No. 47,369
Attorney for Applicants

Jeffrey K. Mills
Registration No. 56,413
Attorney for Applicants